

**THE ASSOCIATION OF SMOKE EXPOSURE AND TUBERCULOSIS IN
SASKATCHEWAN**

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Graduate Studies and Research
in Partial Fulfillment of the Requirements
for the Degree of Master of Science
in the Department of Community Health and Epidemiology
University of Saskatchewan
Saskatoon

By

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Abstract

This cross-sectional study observed the association of smoke exposure and tuberculosis-related outcomes in Saskatchewan by individuals who had been exposed to someone with infectious TB. This study is unique in that we were quantifying the amount of smoke exposure that increases susceptibility to TB infection and/or active TB. Subjects who were at least 18 years old were enrolled into the study because they were contacts to infectious tuberculosis. The study involved a detailed interview. This interview involved questions on demographics, hair treatment (specifically, hair dyeing), tobacco smoke exposure, co-morbidities/risk factors, and alcohol consumption. After the interview was conducted, a small 10mg sample of hair was collected from each individual. This was to ensure a more accurate level of smoke exposure was attained. In total, 104 individuals were recruited to participate in this study. Linear regression analysis was used to compare cigarette consumption and nicotine concentration. A quadratic term was added to the linear model and the result was that reported cigarette consumption per day (x) was significantly associated with nicotine concentration (y) where $y=0.91+1.35x-0.25x^2$ ($p=0.001$). A Fisher's exact test was conducted to see if there was a relationship between smoking and TB disease; there was no statistically significant association between TB disease and smoking (OR= 3.28, 95%CI 0.37-29.1, $p = 0.24$). Logistic regression analysis was used to see if there was a relationship between smoking and TB infection. Of the five predictor variables, none were statistically significant. Smokers had an association with higher odds of TB infection (OR=2.03, 95%CI 0.71-5.80, $p=0.19$). Canadian-born Aboriginals had an association with lower odds of TB infection (OR=0.52, 95%CI 0.18-1.46, $p=0.21$). The results from this study could provide insight into creating a larger, more complex study involving TB and smoking.

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Chapter One: Introduction

1.1 *Study Rationale*

Tuberculosis (TB), a highly complex infectious disease, continues to be a major threat worldwide. The World Health Organization (WHO) estimates that it is the second leading cause of death from infectious disease, after the Human Immunodeficiency Virus (HIV) (1). The WHO approximates that there were 8.6 million new TB cases in 2012, along with 1.3 million deaths from TB. Death from TB can be largely avoided with proper access to health care and treatment. About 90% of cases can be treated with first-line drugs that have been available for decades (1).

In 2011, the incidence of tuberculosis in Saskatchewan was 7.5 per 100,000 population, which was significantly higher than the Canadian incidence of 4.7 per 100,000 population (2). One mechanism, smoking, has been singled out as a risk factor to contracting TB. A high prevalence of tobacco use has been noted since the early 20th century in studies looking for risk factors for tuberculosis. Despite numerous medical advances with tuberculosis, only a limited number of studies have examined the effect that active and passive smoking may have on contracting TB infection and progression to TB disease.

1.2 *Study Purpose*

The purpose of this study is to observe the association of smoke exposure and tuberculosis-related outcomes in Saskatchewan. This study is unique because it examines hair samples from individuals who have been exposed to someone with infectious TB.

This will allow us to compare and analyze the amount of nicotine found in hair samples with smoking history. We hope to be able to see if this has an impact on whether or not someone is more likely to contract a TB infection and/or possibly progress to TB disease. The objective is to support deeper understanding of how smoke exposure affects initial infection and development of TB. The results may be able to improve methods within TB control to prioritize individuals who have been in contact with infectious TB.

1.3 *Research Objectives*

The objective of this research is to investigate the following research questions:

- I. Is there a relationship between nicotine concentration and self-reported cigarette consumption?
- II. Among individuals who have a TB infection, do smokers have a higher chance of developing active tuberculosis than non-smokers?
- IIIa. Are smokers more prone to TB infection than non-smokers?
- IIIb. Do Canadian-born Aboriginals have a higher chance of having a TB infection?

Chapter Two: Literature Review

2.1 Tuberculosis

Tuberculosis (TB) is a complex infectious disease that has affected humans for thousands of years. TB is caused by mycobacteria belonging to the *Mycobacterium tuberculosis* complex. Despite being first identified by Robert Koch in the late 19th century, *Mycobacterium tuberculosis* is still a leading cause of death in low and middle-income countries (1).

Currently, *Mycobacterium tuberculosis* is one of the world's most lethal pathogens; it is estimated that one-third of the world's population is infected with this micro-organism (1). The World Health Organization (WHO) estimates that in 2012, there were 8.6 million incident cases of TB globally (equivalent to 137 cases per 100,000 population)(1). In 2009, there were approximately 14 million prevalent cases of TB disease (equivalent to 200 cases per 100,000 population (3)). There were an estimated 1.6 million deaths due to TB in 2009, making it the second leading cause of death by an infectious disease in the world (3). The large majority of the cases (95%) are in the developing world, where resources and treatments are scarce. The spread of the human immunodeficiency virus (HIV) and the emergence of drug-resistant TB strains threaten to make some cases incurable (4). Both an increase of susceptibility in HIV patients and the emergence of drug-resistant strains have put an enormous burden on health care, forcing health professionals to re-think existing methods of prevention, diagnosis and treatment (4).

Tuberculosis occurs through one main pathway: acquisition of infection followed by progression to disease. Infected individuals are not always ill or infectious, but there is a 10% chance infected individuals will develop TB disease. Individuals who are infected with TB, but do not have the disease are described as having a latent TB infection (LTBI). Individuals who

have TB disease are described as having active tuberculosis and may spread the disease to other people (4).

There are many factors which aid in the development in TB; these are known as risk factors. Some of these factors include HIV/AIDS, Canadian-born Aboriginal status, alcohol use, tobacco smoking, and low socioeconomic status (overcrowding in houses, lower income, lower level of education) (4;5).

HIV plays a major role in the acquisition and development of TB. The Public Health Agency of Canada (PHAC) defines the Human Immunodeficiency Virus (HIV) as a virus that specifically targets and attacks the immune system. HIV leaves individuals with a chronic and progressive illness, where the human immune system becomes vulnerable to infections and cancers (6). Specifically, HIV targets the key part of an individual's immune system, known as the CD4 cells. The HIV virus attacks the CD4 cells by invading them, using the CD4 cells to make more copies of the HIV virus, and then eventually destroys the CD4 cells (7). Once the CD4 count falls below a certain number, the body can no longer fight infections and diseases. When this occurs, the HIV infection can progress to AIDS, which stands for Acquired Immunodeficiency Syndrome (6). AIDS is the final stage of HIV and can result in death if proper treatment is not sought. HIV is an infectious agent, which is transmitted person to person through the individual's bloodstream. HIV can be transmitted from unprotected sexual intercourse, shared needles, unsterilized needles, pregnancy, delivery and breast feeding, and occupational exposure in health care settings (6).

Tuberculosis is one of the leading causes of death among people living with HIV and HIV is one of the strongest risk factors for developing TB disease (8). People living with HIV are 30 times more likely to develop TB than people without HIV (9). According to the World

Health Organization, in 2012 1.1 million of new TB cases worldwide were HIV-positive (9). South Africa is one of the most affected countries because 73% of all TB cases are HIV-positive (8). It is important to highlight the significance of the relationship between TB and HIV when looking at a population.

2.2 Tuberculosis Pathogenesis

TB disease indicates the presence of current active tuberculosis that is usually symptomatic. This is usually defined by either a laboratory confirmed case or a clinically confirmed case (4). Transmission of TB occurs by aerosolized droplets generated by a cough in persons with active disease, that when inhaled by other individuals, infection may be established (10). When infected people cough, sneeze, or even talk, they propel the mycobacteria into the air. To cause an infection, a certain number of mycobacteria need to be inhaled. Nevertheless, not all people who inhale these droplets will get an infection or even get sick. Approximately 10% of individuals infected with *M. tuberculosis* end up developing TB disease (11). Latent tuberculosis infection (LTBI) is defined as infection without either laboratory or clinical evidence of disease (10). LTBI means the individual is infected with *M. Tuberculosis*, but the mycobacteria is dormant (not growing) and there is no evidence of clinically active disease (12). Latent tuberculosis is defined by an immunologic test; the tuberculin skin test or mantoux test (TST) is the standard diagnostic tool for TB infection. The TST is an intradermal injection of tuberculin administered into the forearm to determine if a person has a reaction to tuberculin antigen. A reaction to this test is interpreted to mean that the individual has been exposed to and infected with *M. Tuberculosis*. It is also important to note that not all infected persons will

produce a positive result. The reasons for false-negative reactions are an inability to react to skin tests because of a weakened immune system, recent TB infection, very old TB infection, very young age, recent live-virus vaccination, and incorrect method of TST administration and/or interpretation of result (13). Conversely, a person may produce a false positive reaction due to several reasons. These reasons include, but are not limited to: infection with nontuberculosis mycobacteria, previous BCG vaccination, incorrect method of TST administration and/or interpretation of result (13).

Probability of transmission increases with the following factors: frequency and severity of cough in the individual infected with tuberculosis disease, duration of exposure, proximity to the source case (the individual infected with tuberculosis disease), crowding and poor room ventilation, and delays in diagnosis and/or effective treatment (4).

The state in which the host is able to control the infection, but not completely eradicate the mycobacteria is a representation of equilibrium within the human body (10). The greatest threat to individuals with a latent infection occurs when the immune response fails in some way and the infection reactivates to cause active disease (14). In most cases, the host's immune system is strong enough to forestall active tuberculosis for a lifetime (14).

Tuberculosis is ordinarily classified as pulmonary and non-pulmonary. Pulmonary disease means the tuberculosis is in the lungs and conducting airways. In pulmonary TB, which accounts for most cases of TB, the smear positive patient is considered to spread the infection via an airborne route (15). In less common cases, smear negative pulmonary TB cases can transmit infection to others (12). The term non-pulmonary or extrapulmonary tuberculosis is used to describe the occurrence of TB at sites other than the lung (16). Non-pulmonary TB means the infection can be found in any organs, including the bones, kidneys and meninges of the brain

(15). Non-pulmonary TB will not transmit infection to other people.

2.3 Epidemiology of Tuberculosis

Most Canadians have a low chance of developing active tuberculosis disease. In Canada, the incidence was 4.78 per 100,000 population in 2012 (17). The highest rate in the country was reported in Nunavut, which had a rate of 184.4 per 100,000 population, more than 28 times the national rate (18). Statistics from 2012 highlight that 64% of all reported TB cases in Canada were foreign-born individuals. Canadian-born Aboriginal cases make up approximately 23% of all reported cases in the country, even though they comprise only 3.8% of Canada's population (17). The TB rate in Canadian-born Aboriginals remains the highest of any of the Canadian born groups, being almost 6 times greater than the Canadian average (18).

In 2011, the rate of TB in Saskatchewan was 7.5 per 100,000 population, which was

significantly higher than the 2011 Canadian rate (4.7 per 100,000 population), as illustrated in Figure 1(2).

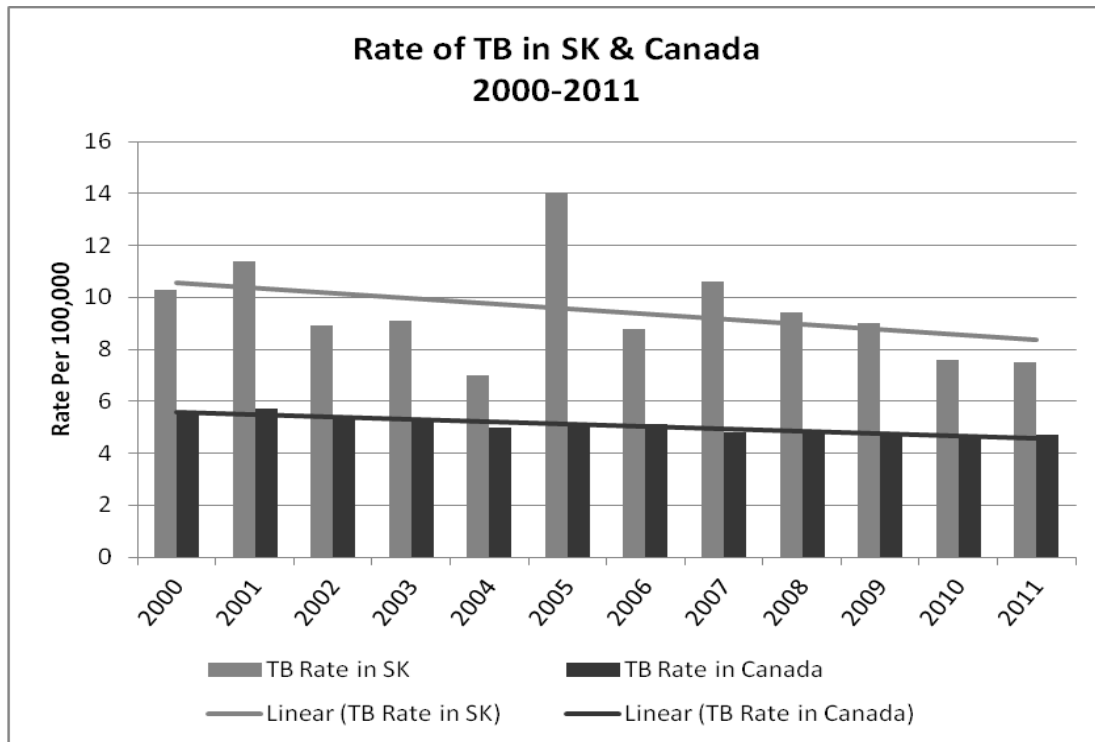


Figure 1. Tuberculosis rate in Saskatchewan and Canada between 2000 and 2011

This figure illustrates the differences between Saskatchewan and Canada. It is clear that SK has a higher rate of TB

than Canada from 2000-2011. Rate per 100,000 is shown on the Y-axis and the year is shown on the X-axis. (Source: Saskatchewan TB prevention and control program)

In Saskatchewan, Canadian-born Aboriginals made up nearly 77% of new cases in 2011, whereas foreign-born individuals made up nearly 19% of new cases. The rate of active TB in Canadian-born Aboriginals is clearly illustrated in Figure 2.

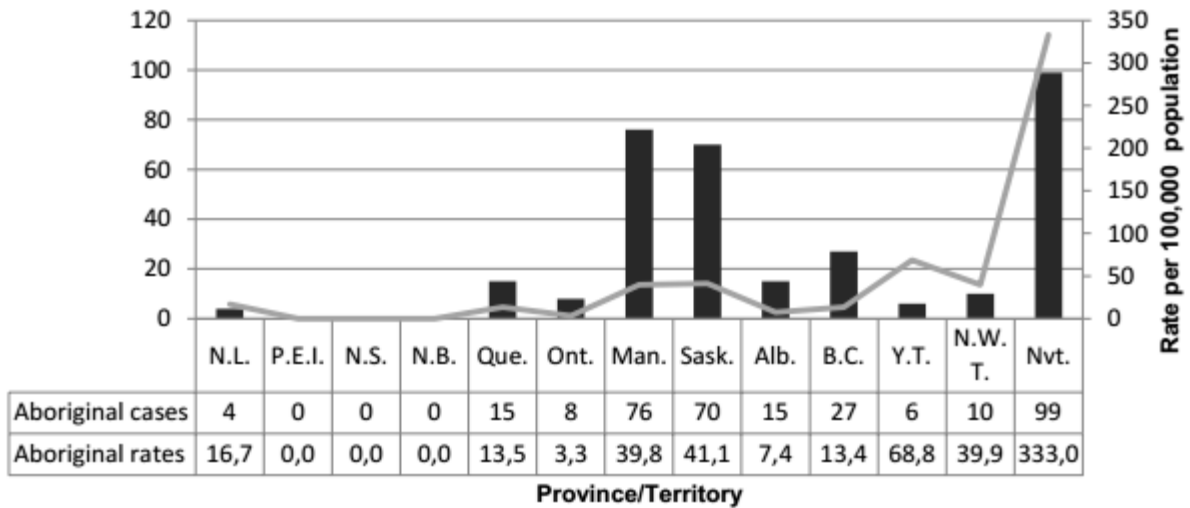


Figure 2. Rate of active TB disease in Canadian-born Aboriginals per province/territory in Canada in 2010

This figure shows the rate of TB per 100,000 on the Y-axis and the rate per province/territory on the X-axis. Manitoba, Saskatchewan, and the Northern territories have high TB rates in the Canadian-born Aboriginal population. Newfoundland, Prince Edward Island, Nova Scotia and New Brunswick all have extremely TB rates in the Canadian-born Aboriginal population. (Source: Public Health Agency of Canada, TB Control Standards, 7th edition)

Saskatchewan, Manitoba, and the Northern Territories have the same characteristic, a high active TB rate in the Canadian-born Aboriginal population.

2.4 Tobacco Smoking

Tobacco is a plant that is native to North and South America (19). It is estimated

that as early as 1 B.C., American Indians began using tobacco in religious ceremonies and part of medicinal practices (20). In the 15th century, Christopher Columbus was offered dried tobacco leaves from the American Indians. Shortly after, tobacco was brought to Europe and the plant was grown all over the world (19). Tobacco was thought to be a cure to most ailments that affected people. As the popularity of tobacco grew, so did its affiliation with politics and finances (21). The lands where tobacco was produced became highly valuable territories, attracting individuals who wanted to make their fortunes, even if it meant living in dangerous conditions (21).

The tobacco smoking pandemic arose at the beginning of the 19th century, when tobacco was being produced commercially throughout the world (22). The birth of the modern cigarette was in 1913, when RJ Reynolds introduced the Camel brand (19). The rise of the manufactured cigarette meant an enormous increase in smokers across the world. It is estimated that, at the beginning of the 21st century, about one third of the world used tobacco (19). Currently, it is thought that nearly a fifth of the world's population smokes tobacco or uses tobacco products (23).

The most common form of tobacco smoking is cigarettes, but there are many other types of products that contain tobacco: pipe tobacco, cigars, cigarillos, sniff, and snus. Tobacco is a plant that are composed of many chemicals including nicotine, chlorophyll, and water (24). The tobacco plant is harvested when it is ripe and the leaves are dried (24). When the leaves begin to dry, this process is known as curing. There are three main methods of curing. The first method is known as flue-curing, which means the tobacco leaves are dried in an enclosed building that contains a heat source (24). The second method involves the tobacco leaves dry in an open-frame building, but are protected from wind and sun: this method is known as air-curing. The

last method is known as sun-curing, which means the tobacco leaves are dried under the rays of the sun. Once the tobacco leaves are cured, they are sold to a processor. The processor then shreds the tobacco and assembles it into a paper filter to produce a cigarette. Tobacco is one of many ingredients that are added to a finished cigarette. There are approximately 600 ingredients in a single cigarette (25).

Tobacco contains a drug called nicotine (26). When a cigarette is smoked, it can take as little as 10 seconds for nicotine to reach the brain (27). This causes three main reactions in the human body: heart rate and blood pressure increase, blood vessels constrict, and muscles relax (27). Nicotine works by imitating acetylcholine, a naturally-occurring neurotransmitter in the human brain (28).

Tobacco smoke contains thousands of chemicals including 43 known carcinogens (29). It is estimated that tobacco smoke contains more than 4,000 compounds in different chemical states (22). There are many known health effects that environmental tobacco smoke exposure causes in both active and passive smokers: lung cancer, heart disease, bronchitis. Tobacco smoke leads to more deaths than any other significant cause, such as alcohol, car accidents, and AIDS (22).

There are two main ways people are exposed to tobacco smoke: either they are actively smoking by inhaling tobacco smoke into the lungs (known as active smokers) or they are indirectly inhaling the air in which tobacco smoke is present (known as passive smokers) (22).

2.4.1 Measuring Smoke Exposure

There are many ways of measuring smoke exposure. Many studies have examined smoke exposure simply by self-reporting tobacco use. Due to the well-documented negative

effects of tobacco use, one study suggested active smokers are likely to under-report their tobacco use (reporting bias) (30). Nevertheless, one survey conducted by Statistics Canada noted that self-reporting data on smoking status provided a valid estimate of the prevalence of smoking in Canada (31). One study suggests using a biomechemical validation of self-reported tobacco use to decrease distortion between self-reported cigarette consumption and actual cigarette consumption (32). To account for this, this study looked at both nicotine levels in hair and self-reported tobacco use to estimate how much smoke an individual was exposed to.

2.5 Epidemiology of Tobacco Smoking

The World Health Organization believes that tobacco use continues to be the leading global cause of preventable death, while costing hundreds of billions of dollars of economic damage each year (33). The WHO estimates that smoking causes 9% of deaths worldwide (34). It is estimated that nearly 1.3 billion people smoke tobacco products (34). Most of these people live in low or middle income countries, where the burden of TB is very high.

Tobacco continues to kill six million people each year and an additional 600,000 non-smokers who die from second-hand smoke exposure (35). If current trends continue, the WHO estimates that, in the 21st century, tobacco will be the cause of over a billion deaths worldwide (33).

In 1999, 25.2% of Canadians were considered current smokers. In 2012, approximately 16.1% or 4.6 million Canadians were current smokers (36). This trend is representative of the past 50 years in Canada; in the mid 1960's, over 60% of Canadians were current smokers, which is over three times as many smokers as there are now.

The 2013 Canadian tobacco report suggests there were 3.4 million daily smokers (11.9%) and 1.2 million non-daily smokers (4.2%). Smoking was highest among young adults aged 20-24 (20.3%) and 25-34 (21.8%). It also appears that smoking is more prevalent in males (18.4%) than females (13.9%) (37).

Among the Canadian provinces, Newfoundland had the highest smoking rate with a prevalence of 19.7%, while British Columbia had the lowest smoking rate at 13.2%. The daily average cigarette consumption (cigarettes per day, CPD) ranged from 15.8 in Ontario to 12.9 in British Columbia. Approximately 18.5% of Saskatchewan residents were smokers in 2012, above the 2012 national average of 16.1% (36). On average, Saskatchewan consumed 13.8 cigarettes per day. This is a decrease from the 2011, where 19.2% of Saskatchewan residents were current smokers and the average cigarettes consumed per day was 14.8. According to 2008 data, the lowest smoking rates in Saskatchewan were found in Cypress (21.1%) and the highest smoking rates were found in Mamawetan/Keewatin/Athabasca (41.3%), Sunrise (26.9%) and Sun Country (29.9%) (38).

In 2009, it was estimated that tobacco use costed the Saskatchewan economy in \$167.6 million in direct health care costs; it was also estimated that tobacco use costed \$535.2 million in indirect costs, such as loss in productivity and short-term disability (38). There are numerous additional costs tobacco use costs the Saskatchewan economy. The full cost of tobacco use in Saskatchewan in 2008 was estimated at \$1.08 billion. Only a small fraction (18%) of these costs was offset through tobacco tax revenue. About 34% of the cost was covered by Saskatchewan employers and 48% was covered by tax payers.

2.6 *Smoking and Tuberculosis*

Smoking has long since been identified as an increased risk for both TB infection and TB disease. In 1842, Chadwick noted “tuberculosis thrives in deprived bodies: its allies are undernourishment, debilitation, unventilated living and working accommodation, squalor, and smoking” (39). Following Chadwick’s statement, doctors and researchers formed an opinion that tobacco smoking caused inflammation in the lungs, which increased the opportunity for bacterial infection (40). This led them to believe that smokers were at a higher risk for tuberculosis infection and disease. We now recognize the greater susceptibility of smokers to TB reflects three main factors: smoking damages the lungs, which makes individuals more susceptible to TB infection; smoking harms the immune system, which makes individuals less likely to combat TB infection; and smoking reduces the effectiveness of TB treatments, which could result in longer periods of infection or more severe disease (41). Research has shown that both active and passive smoking can affect how someone becomes infected with TB bacteria and how the infection progresses to TB disease (42-44).

There have been a number of researchers that have found that active smoking increases susceptibility to tuberculosis (42;43;45). One study concluded that tobacco smoking was associated with a twofold increased risk of active tuberculosis in a general Taiwanese population (42). According to Basu et al., smoking increases the risk of latent tuberculosis by 1.9, active tuberculosis by 2.0, and death from tuberculosis by 2.6, after adjusting for socioeconomic status (23). The same study presented a mathematical model projecting that a total of 113 million tuberculosis cases and 88 million deaths from tuberculosis would be attributable to smoking between 2010 and 2050 (23). One systematic review and meta-analysis conducted looked at

several variables, including tobacco smoking as an implicated risk factor for TB infection, disease and death. They found that there is consistent evidence that tobacco smoking is associated with an increased risk of TB (46). The increased risk of latent TB for smoking compared with non-smoking is illustrated thoroughly in this article. The meta-analysis specifically looked at 1 case control study and 5 cross-sectional studies, all of which showed an increased risk of latent TB infection for smoking compared with non-smoking. The odds ratio for all these studies ranged from 1.72 to 3.2, with very narrow confidence intervals. This conveys that a significant, positive relationship was found in all of the studies. One of the study's weaknesses was that they did not control for antigen exposure. This would provide key insight by analyzing how much antigen individuals were exposed to, which would either increase or decrease their risk of contracting a latent TB infection.

Passive smoking has also been analyzed by researchers as a risk factor for TB. One study concluded that passive exposure to tobacco smoke within the household was found to be an independent predictor of the development of active TB among a cohort of never-smoking married women aged 65 to 74 years (44). They also stated that passive smoking accounted for 13.7% of active TB cases in this cohort. One meta-analysis also examined the impact of passive smoking on developing TB disease. They found that passive smoke exposure substantially increased the risk of developing TB disease compared with non-exposure. The meta-analysis specifically looked at case control studies in adults and in children. It found that the risk of clinical TB disease for passive smoking exposure was significant when compared to non-exposure. In fact, the studies looking at children and passive smoking found very high odds ratio with very narrow confidence intervals. This means that there is a positive and significant relationship between passive smoking and risk of clinical TB disease.

Although smoking cessation has not been as widely researched, one study offered some interesting insight. This study looked at smokers in China who had already been diagnosed with TB. They found that smokers had a very high TB mortality, almost as high as nine times than those who had never smoked. Upon smoking cessation, the risk reduced significantly and was similar with those who never had smoked (47). This study estimated that the TB mortality rate reduced nearly 65% when people quit smoking (44).

Chapter Three: Methodology

3.1 Study Design

This study is a cross-sectional study. The population used for this study were individuals in Saskatoon, Saskatchewan who had been in contact with someone with infectious tuberculosis. The samples that were drawn from this population were all over the age of 18 and had been labelled “at-risk” because they were exposed to infectious TB. In total, 104 subjects were recruited and many variables were assessed. An interview and hair sample was collected with each subject who agreed to participate in the study. The interview was composed of questions on demographics, risk factors/co-morbidities, and alcohol consumption. Subjects were at least 18-years-old and were enrolled into the study because they were contacts to an infectious tuberculosis case. According to the Saskatchewan TB Prevention and Control Program, a contact is defined as “individuals who have breathed the same indoor air ten hours or more one month prior to the date of diagnosis of a person with [infectious] tuberculosis; the emphasis is on the time and proximity of exposure” (12).

3.2 Setting and Population

The setting for this study was the city of Saskatoon, Saskatchewan’s most populous urban centre, with an estimated population of 246,300 as of June 30th, 2013 (48). The study population were individuals who were a contact of someone with infectious tuberculosis. Subjects would either be seen in the TB control clinic in the Royal University Hospital or outside the hospital in Saskatoon. Participants were collected between July 2012 and August 2013. Individuals who

were excluded from the study was anyone under the age of 18.

3.3 *Ethics Approval*

This study was initially approved by the Biomedical Review Ethics Board at the University of Saskatchewan in June of 2011. Amendments were made to add Kelsey Seal as a co-investigator in summer of 2012. A second amendment was made in late spring 2013, allowing the co-investigator(s) to follow the nurse conducting contract traces outside of the hospital.

3.4 *Data Collection*

As previously mentioned, data collection took place both inside the Royal University Hospital and in the field, with somewhat different subpopulations associated with each of these venues. As part of their standard contract tracing process, TB control personnel notified any contacts that have been in close proximity with an individual with diagnosed TB disease. Contacts are usually tested in one of two ways: either these individuals are called to the TB Control clinic to receive a TST or the public health nurse may also venture into the field to test using TSTs. There are certain all day clinics in TB control where the TB doctor meets with individuals who either have LTBI or TB disease.

As part of data collection, the Master's student would come to the clinic days and attend field clinics. The TB nurse would let the Master's student know when they were venturing out into

the field to plant¹ TST's or holding a clinic day. While planting TST's, the nurse would tell the possible participant about the study and if they were interested, they could participate after their TST was read (approximately 48 hours after the TST was planted). This was to ensure that the TB control program would have their TST result and that information required for the study would be collected. If their reaction measured 5mm or more, they were considered to have a positive TST; this is the accepted practice amongst TB health professionals (4). Once their results had been read by the TB nurse and they were marked as a potential participant, the nurse would then briefly explain the study. If the participant conveyed their interest and agreed to the study, the Master's student was introduced to the participant. Informed consent was then sought by signing the participant information and consent form. After the consent form was read and signed by the participant, the first component of the study involved a detailed interview. This interview involved questions on demographics (age, education level, ethnicity, housing situation), hair treatment (hair dyeing), tobacco smoke exposure, co-morbidities/risk factors, liver disease, and alcohol consumption. After the interview was conducted, the Master's student took a small (approximately 10mg) sample of the patient's hair. The hair was extracted with a set of scissors and was cut as close to the scalp as possible. The hair was placed in a marked envelope, sealed, and stored in a secure area. The envelopes had a number placed on them to ensure the participants remained anonymous to everyone but the Master's student. The participant was then thanked for their time and an incentive was given to cover basic expenses (such as time and/or cost of travel).

¹ To "plant" is to administer an injection.

3.5 Hair as a Biomarker to Measure Smoke Exposure

Biomarkers are becoming a standard for measuring environmental tobacco smoke exposure, as they avoid many sources of bias (49). A biomarker is defined as a biological molecule used to measure signs of a normal or abnormal process in the human body (50). Doses of exposure to environmental smoke are calculated by the analysis of toxic substances in biological specimens (22). There are two main types of monitoring exposure: real-time monitoring, which determines exposure at any given instant, and which evaluates trace substances in samples of blood, urine, saliva, breast milk, and placenta, and long-time monitoring, which determines exposure over a long period of time and which evaluate substances in hair, bones, liver, and fatty tissue (22).

Urine cotinine is one of the more widely used biomarkers to measure environmental tobacco smoke exposure. Measuring urine cotinine has its disadvantages, which include variability in cotinine excretion levels for similar tobacco exposures and a short half-life of 20 hours (49).

Hair nicotine is acknowledged as a more accurate biomarker of environmental tobacco smoke exposure than urine cotinine. Although cotinine is present in hair, it exists at much lower concentrations than nicotine. The lower cotinine level in hair can make it extremely difficult to differentiate between active and passive smoke exposure groups (49). Nicotine is incorporated into hair if it is present in the circulation and contamination of nicotine is minimal after washing samples (51). Alternatively, some scientists argue that nicotine is mainly absorbed into the hair from the ambient environment (52). Advantages of using hair nicotine as a biomarker include its

capacity to record longer-term exposure patterns, collection ease, storage at room temperature without degradation for up to 5 years, and shipment without any necessary precaution (51).

One study noted that self-reported tobacco use was better correlated with salivary cotinine levels than hair nicotine levels. Moreover, a survey conducted by Statistics Canada found a significant association between urinary cotinine and self-reported cigarette consumption. This is probably because salivary cotinine represents relatively recent exposure levels, as opposed to hair nicotine which is a longer-term biomarker (30).

Hair nicotine has been established as an effective biomarker to determine tobacco smoke exposure. The most popular way to measure nicotine in hair is high-performance liquid chromatography (HPLC). This is found to be a cheaper and easier means of measuring nicotine in hair compared to the alternatives (53).

Hair samples were collected by cutting hair from the base of the scalp and storing the hair in paper envelopes. The hair was submerged in different chemicals for a specific period of time. The samples were then inserted into a tube using a machine called an electronic balance and then washed for 90 minutes in a solvent called dichloromethane. The samples were then dried. The hair was then digested by placing the samples in tubes of sodium hydroxide. Nicotine was extracted from the digest with diethyl ether. The nicotine was measured using an electrochemical detector (53).

3.6 Variables

In this study, several variables were analyzed. The following is a complete list of variables used:

TB information

- *TST Result*: The TST is used to see if an individual has been infected with TB. A positive test (meaning exposure was detected) is defined as an induration that is 5 mm or more in diameter; this measurement is the Canadian Standard for contacts to infectious tuberculosis and used by the Saskatoon Health Region. This continuous variable was obtained through the Tuberculosis Information Database. Every patient that is given a TST has their results entered into the Tuberculosis Information Database, regardless whether there is a positive or negative outcome.
- *TB Disease*: This categorical variable was obtained through the TB database. It is a variable that is also recorded in the database as “Yes” or “No”.

Demographics

- *Participant seen in the Clinic or Field*: This dichotomous variable was determined at the time of interview.
- *Date of Birth*: Birth date was the first question asked in the interview, but could also be found using the TB data base. It is a continuous variable.
- *Age at the time of Interview*: This is a continuous variable that was obtained during the interview. In this study, no one under the age of 18 was recruited.
- *Gender*: Gender was a dichotomous question asked on the interview.

- *Ethnicity*: This categorical variable was obtained through the interview. There were five possible ethnicities that could be selected: Canadian-born Aboriginal (comprised of Métis, Inuit, and First Nation), Canadian-born Non-Aboriginal, and Foreign-born.
- *Education Level*: Education level was one of the first categorical questions asked on the interview. There were three choices: elementary, secondary, and university/college.
- *Hair Treatment*: Everyone who was interviewed was asked if they had dyed their hair in the past 6 months. This is because hair dye can have a significant impact on nicotine concentration in the strands of hair. This is a categorical variable.
- *How much do you smoke*: This categorical variable was obtained through the interview. There were three possible choices: daily, less than daily, and never.
- *Have you smoked daily in the past*: Anyone who answered “less than daily” or “never” to the question “how much do you smoke?” was asked “have you ever smoked daily in the past?” This variable is dichotomous.
- *How long since you last had a cigarette*: This continuous question was asked to individuals who said they were daily smokers in the past, but are not currently daily smokers.
- *How old were you when you first started smoking*: This continuous question was obtained through the interview.
- *How many cigarettes do you smoke a day*: Anyone who said they were a daily or less than daily smoker was asked this continuous question.
- *How often are you exposed to the tobacco smoke of others*: This categorical question was presented to everyone in the study. There were five possible answers: not at all, a few

times per day on some days, many times per day on some days, a few times per day on most days, and many times per day on most days.

- *Do you use smokeless tobacco:* This categorical question was asked of everyone. There were three possible answers: daily, less than daily, or not at all.
- *How many rooms other than closets/bathrooms/storage space are there in your current dwelling:* This continuous variable was asked to get an idea about overcrowding. It was followed by the next continuous question: *How many people in total currently reside in your dwelling?*

Co-Morbidities/Risk Factors

- *Have you ever been diagnosed with a liver condition including hepatitis, liver cirrhosis, cancer, and jaundice:* This dichotomous question was asked from everyone. If the participant responded “yes”, they were asked what specific condition they had.
- *Have you ever been diagnosed with diabetes:* This dichotomous question was asked of everyone. If the participant responded with “yes”, they were asked what type of diabetes they had and how old they were when they were first diagnosed with diabetes.
- *Have you ever been diagnosed with a kidney disease:* This dichotomous question followed any questions about diabetes. If the participant answered “yes”, they were asked what condition they had.
- *Have you been diagnosed or been informed by a health professional that you have any other health conditions such as high blood pressure, heart problems, chronic bronchitis, chronic obstructive pulmonary disease:* This question is dichotomous and it was asked of everyone. If someone responded “yes” to the question, they were asked what specific condition they had.

Alcohol Consumption

- *During the past 12 months, have you had a drink of beer, wine, liquor or any other alcoholic beverage:* This dichotomous question was asked of everyone. If someone responded no, the interview would end here.
- *During the past 12 months, how often did you drink alcoholic beverages:* This categorical question had 7 possible answers: less than once a month, once a month, 2 to 3 times a month, once a week, 2 to 3 times a week, 4 to 6 times a week, or every day.
- *How often in the past 12 months have you had 5 or more drinks on one occasion:* This categorical question had 6 possible answers: never, less than once a month, once a month, 2 to 3 times a month, once a week, or more than once a week.

3.7 Inclusion/Exclusion Criteria

Anyone who was part of a contact trace between July 2012 and September 2013 were eligible for inclusion in this study. Subjects had to have been in contact with someone who had infectious TB, putting the subjects at risk for contracting LTBI. Additionally, anyone under the age of 18 was excluded from this study.

Inclusion criteria:

- i. Any person who was in contact with the index case (client with infectious TB, which lead to the investigation of contacts).
- ii. Any person living in Saskatchewan.

Exclusion criteria:

- i. Individuals who were under the age of 18 at the time of interview.
- ii. Individuals who did not have enough hair to collect for an adequate sample.

3.8 Data Analysis

Univariate, bivariate, and multivariable data analyses were performed to satisfy each of the research questions. All data was processed using SPSS 21.0 and Microsoft Excel.

The difference in nicotine concentration between smokers and non-smokers was examined using a Wilcoxon Rank Sum test. Nicotine Concentration between smokers/non-smokers and individuals who dye their hair and do not dye their hair was also examined using a Kruskal Wallis test. This was to see if hair dyeing had an impact on nicotine concentration.

Research Question 1: Is there a relationship between self-reported cigarette consumption

and nicotine concentration? Linear regression was used to assess the relationship between cigarettes smoked per day and nicotine concentration in all study participants. The association was examined to see if it met the linearity assumption and then the regression residuals were examined for normality, homogeneity of variance, and for the presence of extreme outliers and influential observations.

Research Question 2: Among individuals who have a TB infection, do smokers have a

higher chance of developing active tuberculosis than non-smokers? Because of the extremely low number of people who developed active TB, a Fisher's exact test was conducted. The relative risk and exact 95% confidence intervals were calculated using EpiInfo version 7.1.4

(Centers for Disease Control, Atlanta, Georgia). Due to the very small number of cases, there was no attempt to adjust for potential confounders.

Research Question 3a: Are smokers more prone to TB infection than non-smokers?

Research Question 3b: Do Canadian-born Aboriginals have a higher chance of having a TB infection? One individual who had an unknown TST result was omitted from this analysis.

Multivariable logistic regression approach was used to assess the association between smoking, Aboriginal status and the risk of a positive TST result for TB. To begin, a series of univariate logistic regressions were conducted using TB infection as the outcome variable to screen potential risk factors of interest; variables associated with TB infection with p-values ≤ 0.25 became candidates for multivariable modelling. TB infection (yes/no) was examined to see if it was unconditionally associated with several potential risk factors of interest: smoking (created as a dichotomous variable: non-smoker/smoker), aboriginal status (created as a dichotomous variable: Canadian-born Aboriginal/Non-Aboriginal), education (created as a dichotomous variable: elementary education/secondary and post-secondary education), housing density (created as a dichotomous variable: anything 0.5 (Canadian average (54)) or below people per room (PPR) was considered low density and anything above 0.5 PPR was considered high density), hair dye (created as a dichotomous variable: dyes their hair/does not dye their hair), alcohol consumption (created as a dichotomous variable: heavy alcohol consumption/light or no alcohol consumption, based on responses in the questionnaire on frequency and how much they drink), and gender (created as a dichotomous variable: female/male). Age was examined as a continuous variable. Housing density was calculated by dividing the number of individuals in a household by the number of rooms in living quarters, not including storage space and bathrooms. It is a density calculated in persons per room (PPR).

The variables that met the selection criterion at the first stage ($p\text{-value} \leq 0.25$) were entered into the multivariable logistic regression model, along with variables which were of primary interest in the research question (smoking and aboriginal status) to form the preliminary main effects model. Variables with $p\text{-values} \leq 0.05$ in the preliminary main effects model and the variables of primary interest were retained to form the main effects model. Confounding was assessed by a sequential process that was carried out in order to assess the meaningful changes in beta coefficients. If the regression coefficient for the two variables of interest (smoking and Aboriginal status) changed by more than 10% when another risk factor was removed from the model, it was retained as a confounder. Effect modification/interaction was then assessed by individually entering product terms into the main effects model. Interaction terms were retained in the model if the $p\text{-value}$ of the interaction term was ≤ 0.05 . The combination of variables and interactions after this step formed the final model.

Chapter Four: Results

4.1 *Descriptive Statistics*

Out of the 104 individuals used for the study, the plurality self-identified themselves as Canadian-born Aboriginals (47%); 36 identified themselves as Canadian-born Non-Aboriginal (35%) and 19 (18%) identified themselves as Foreign-born. Aboriginal peoples of Canada are indigenous people comprised of First Nations, Métis, and Inuit.

Among all subjects, the prevalence of TB disease was 3.8% (4/104). There were 4 cases of tuberculosis; all 4 cases of TB occurred in people who self-identified themselves as Canadian-born Aboriginal. Out of the 104 cases in the study, 57 (55%) individuals were TST negative, 46 (44%) were TST positive and 1 (1%) case was unknown. Among individuals who tested positive to the TST were 11 (24%) Canadian-born Non-Aboriginal, 19 (41%) Canadian-born Aboriginal, and 16 (35%) Foreign-born.

Education level was another variable assessed in this study. Nearly half (48%) of the people in this study had completed a secondary education.

The youngest person in this study was 18 years old and the oldest person in this study was 72. The mean age for this study was 31.7 years, with a median age of 30.1 (SD \pm 13). There were 59 (57%) female and 45 (43%) male participants in this study.

About 64 individuals (61%) reported smoking cigarettes daily and 40 individuals (39%) reported that they were non-smokers. Among daily smokers, the mean of cigarettes smoked daily was 12, with a median of 10 (SD \pm 9.2). The least amount of cigarette(s) someone reported

smoking was 1 cigarette/day and the highest amount of cigarettes was 50 cigarettes/day. For nicotine concentration among all participants, the mean was 7.2ng/mg with a median of 1.6ng/mg (SD ± 12.6). Nicotine concentration ranged from <0.04ng/mg to 58.97ng/mg.

There were 5 cases of HIV in the population, 12 cases of HCV (Hepatitis C), and 5 cases of HIV/HCV.

Alcohol consumption was another variable used in this study. There were 27 people (27%) of the population who reported that they never consume alcohol. There were 22 (21%) of individuals who said they consumed alcohol less than once a month, 16 (15%) of individuals who consumed alcohol once a month, 10 (9.5%) who said they drink alcohol 2-3 times a month, 4 (4%) of individuals who consumed alcohol once a week, and 7 (7%) who said they drink alcohol more than once a week.

Table 2. List of variables in the study (n=104)

		Number	% of Population
Ethnicity	Canadian-born Aboriginal	49	47%
	Canadian-born Non-Aboriginal	36	35%
	Foreign-born	19	18%
TB Disease	Yes	4	4%
	No	100	96%
TST Result	Positive	46	44%
	Negative	57	55%
	Unknown	1	1%

Education Level	Elementary	28	27%
	Secondary	50	48%
	Post-Secondary	26	25%
Age	Under 25	36	35%
	25-44	47	45%
	45+	21	20%
Gender	Female	59	57%
	Male	45	43%
Cigarette Smoking	Active Smokers	64	61%
	Passive smokers	32	31%
	Non-smokers	8	8%
Comorbidities	HIV/No HCV	5	5%
	HCV (Hepatitis C)/No HIV	12	12%
	HIV/HCV	5	5%
	Neither HIV nor HCV	82	79%
Alcohol Consumption	High Consumption	31	29%
	Low Consumption	73	71%
Housing Density	High	80	77%
	Low	24	23%
Nicotine Concentration (ng/mg)	High (10+ ng/mg)	24	23%
	Moderate (2-10ng/mg)	25	24%
	Low (Less than 2ng/mg)	55	57%

Nicotine concentration was higher in smokers than in non-smokers ($p=0.001$) (Figure 3).

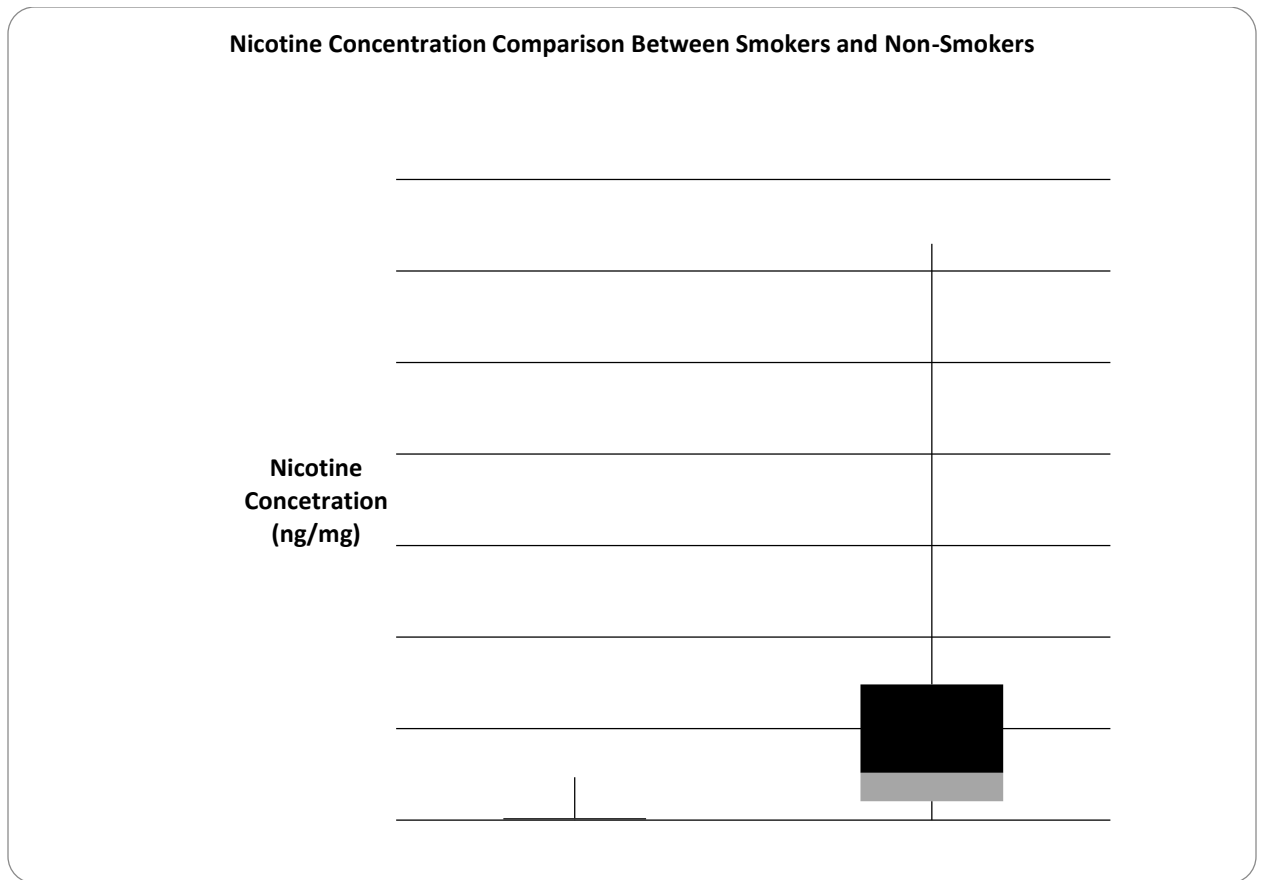


Figure 3. Comparison of nicotine concentration (ng/mg) between smokers and non-smokers (n=104)

Smokers range: 0.026ng/mg-62.93ng/mg; Non-smokers range: 0.006ng/mg-4.68ng/mg

A comparison of nicotine concentration in non-smokers was also observed. Individuals who reported they were exposed to secondhand smoke were classified as having passive smoke exposure. Individuals who reported they were not exposed to secondhand smoke were classified as having no passive smoke exposure. After visual inspection of a boxplot between these two groups in Figure 4, there appears to be substantial difference in nicotine concentration between individuals who are exposed to secondhand smoke and individuals who are not.

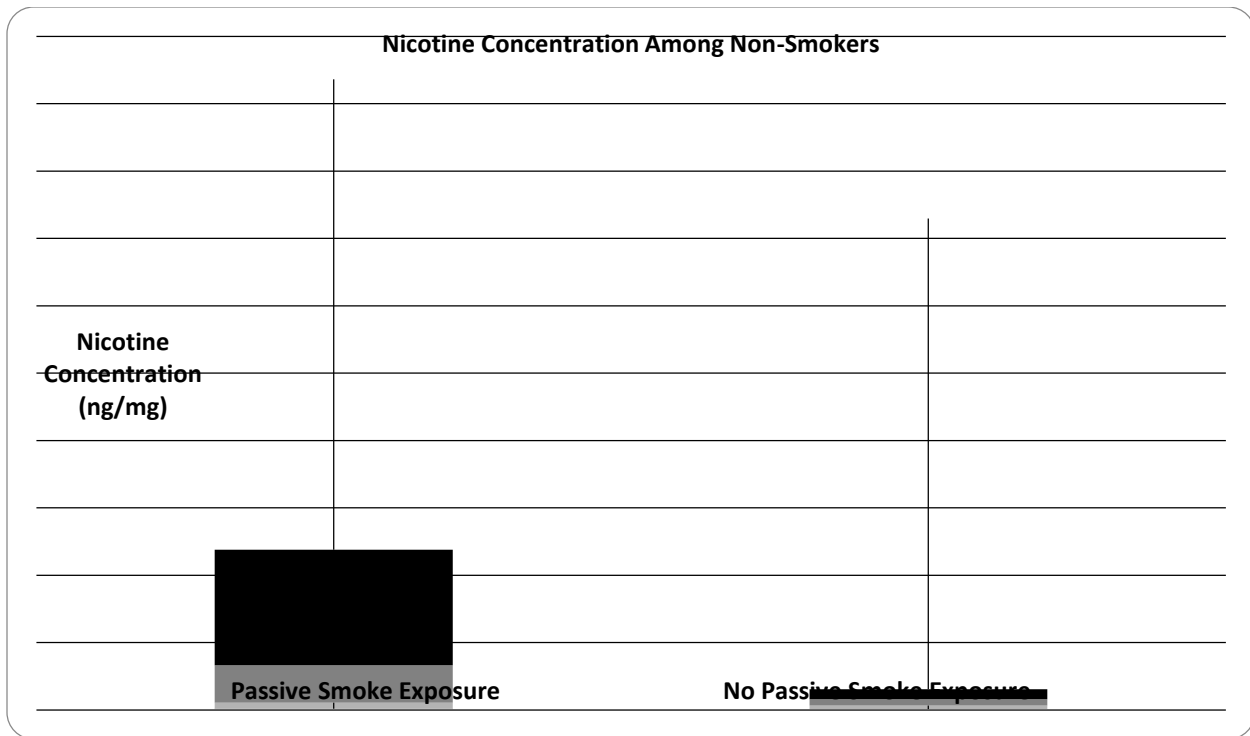


Figure 4. Nicotine Concentration Among Non-Smokers (n=39)

Passive smoke exposure range: 0.01ng/mg-4.68ng/mg; No passive smoke exposure range: 0.01ng/mg-0.9ng/mg

The difference between nicotine concentration in people reporting use of hair dye and no hair dye can be seen in Figure 5. A Kruskal Wallis test showed that the differences between the groups were significantly different from each other ($p=0.001$). A Wilcoxon test determined there was no significant difference between non-smokers who dyed their hair and non-smokers who did not die their hair ($p=0.78$), but there was a significant difference between smokers who dyed their hair and smokers who did not dye their hair ($p=0.02$).

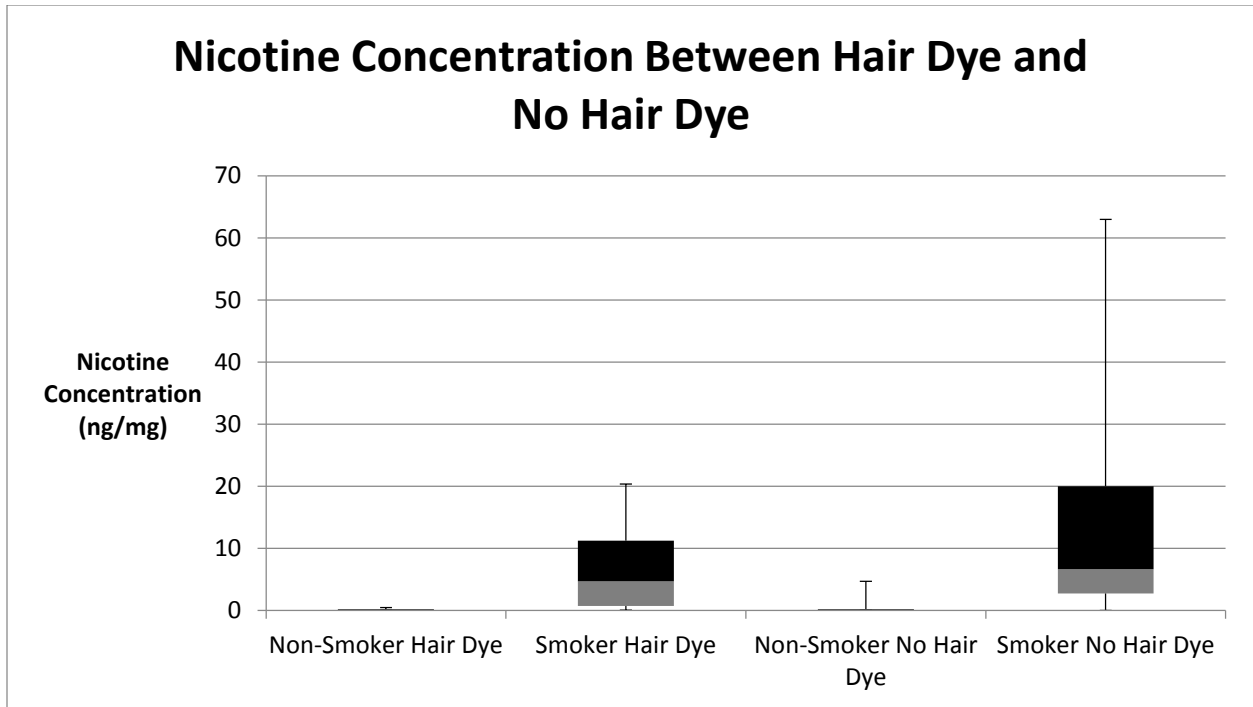


Figure 5. Hair nicotine concentration compared between people who dye their hair and those who do not dye their hair (n=104)

Non-smoker hair dye range: 0.006ng/mg-0.440ng/mg; Smoker hair dye range: 0.045ng/mg-20.374ng/mg

Non-smoker no hair dye range: 0.01ng/mg-4.68ng/mg; Smoker no hair dye range: 0.026ng/mg-62.963ng/mg

The mean housing density in this study was 1.12, the median was 1.00. In figure 6, we see a boxplot comparing housing density among the different ethnicities.

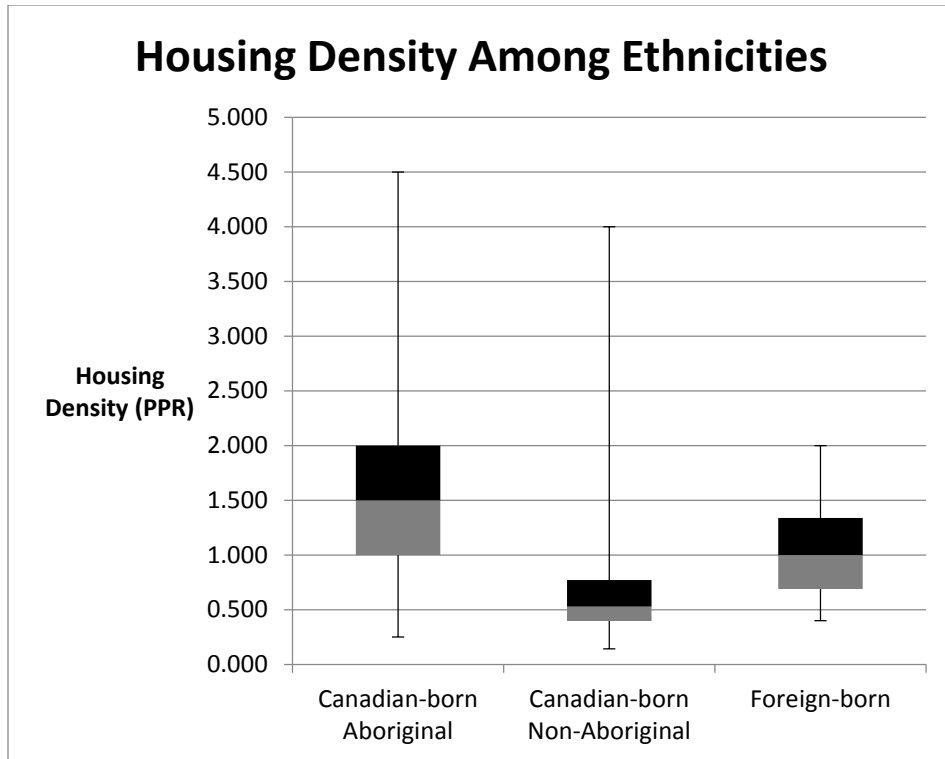


Figure 6. Housing densities among different ethnicities measured in PPR (Persons Per Room) (n=104)

Canadian-born Aboriginal range: 0.250PPR-4.500PPR;

Canadian-born Non-Aboriginal range: 0.143PPR-4.0PPR;

Foreign-born range: 0.40PPR-2.00PPR

4.2 Research Questions

Question 1: Is there a relationship between nicotine concentration and self-reported cigarette consumption?

The association between nicotine concentration and cigarettes consumed per day was not linear.

A quadratic term was added to the linear model and the result was that reported cigarette consumption per day (x) was significantly associated with nicotine concentration (y), where $y=0.91+1.35x-0.25x^2$ ($p=0.001$).

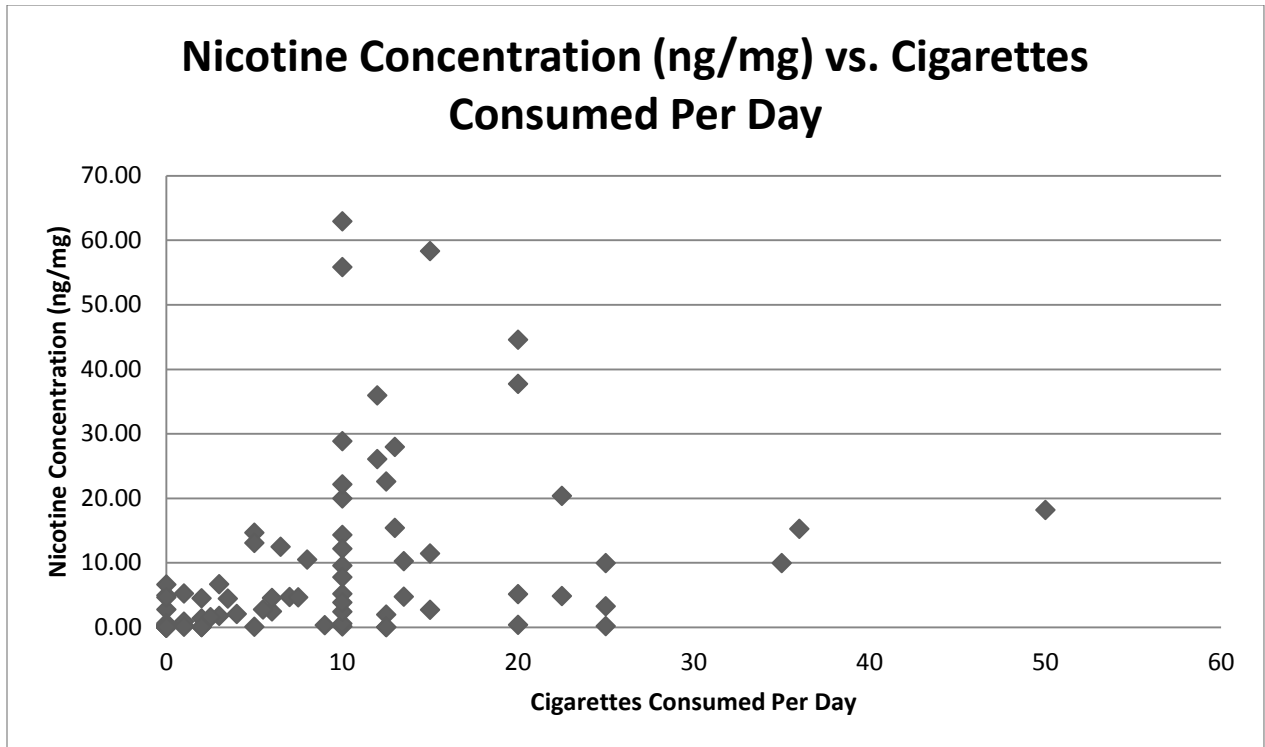


Figure 7. Bivariate Scatterplot of Nicotine Concentration (ng/mg) vs. Cigarettes Consumed Per Day (n=104)

Question 2: Among individuals who have a TB infection, do smokers have a higher chance of developing active tuberculosis than non-smokers?

A Fisher's exact test was conducted between smoking and TB disease as some expected cell frequencies were less than five, so a chi-square test could not be performed. There was no statistically significant association between TB disease and smoking (OR= 3.28, 95%CI 0.37-29.1, $p = 0.24$).

Question 3a: Are smokers more prone to TB infection than non-smokers?

Question 3b: Do Canadian-born Aboriginals have a higher chance of having a TB infection?

Univariate logistic regression was used to identify potential risk factors unconditionally associated with TB infection with a p-value of ≤ 0.25 for consideration in building the final multivariable model.

Table 3. Bivariate logistic regression between TB infection and select covariates (n=103)

	Odds Ratio	95% Confidence Interval	<u>p value</u>
<i>Smoking Status</i>			
<i>Smoker</i>	1.52	0.68-3.38	0.31
<i>Non-Smoker</i>	reference category		
<i>Aboriginal status</i>			
<i>Aboriginal</i>	0.57	0.26-1.25	0.16*
<i>Non-Aboriginal</i>	reference category		
<i>Education</i>			
<i>Elementary Education</i>	1.73	0.72-4.2	0.22*
<i>Secondary/Post-secondary Education</i>	reference category		
<i>Housing Density</i>			
<i>Low Density</i>	reference category		
<i>High Density</i>	1.11	0.48-2.6	0.80
<i>Hair Dying</i>			
<i>Hair Dye</i>	3.27	1.29-8.24	<0.05*
<i>No Hair Dye</i>	reference category		

<i>Alcohol Consumption</i>			
<i>Low/No Alcohol Consumption</i>	reference category		
<i>High Alcohol Consumption</i>	1.90	0.81-4.48	0.14*
<i>Gender</i>			
<i>Female</i>	0.54	0.25-1.20	0.13*
<i>Male</i>	reference category		
<i>Age (years)</i>	1.00	0.97-1.03	0.87
<i>Nicotine Concentration (ng/mg)</i>	1.00	0.97-1.03	0.98

*= Statistically significant at $\alpha=0.25$

Education, hair dye, alcohol consumption, and gender were all retained for consideration in building the final multivariable model to estimate the association between aboriginal status and smoking on TB infection. Smoking status was kept as the measure of smoke exposure, as it had a better fit with TB infection than nicotine concentration, as determined by the p-value. Step 1 in developing the main effects multivariable model estimating the association between Aboriginal status and smoking on the risk of TB infection is summarized in Table 3.

Table 4. Step 1 in developing the main effects model of potential risk factors for TB infection including reported smoking and Aboriginal status (n=103)

	Adjusted Odds Ratio	95% Confidence Interval	<u>p value</u>
<i>Smoking Status</i>			
<i>Smoker</i>	2.08	0.73-6.00	0.17
<i>Non-Smoker</i>	reference category		

<i>Aboriginal Status</i>			
<i>Aboriginal</i>	0.50	0.18-1.43	0.20
<i>Non-Aboriginal</i>	reference category		
<i>Education</i>			
<i>Elementary Education</i>	2.71	0.93-7.90	0.07
<i>Secondary/Post-Secondary Education</i>	reference category		
<i>Hair Dying</i>			
<i>Hair Dye</i>	2.62	0.92-7.50	0.07
<i>No Hair Dye</i>	reference category		
<i>Alcohol Consumption</i>			
<i>Low/No Alcohol Consumption</i>	2.56	0.98-6.67	0.06
<i>High Alcohol Consumption</i>	reference category		
<i>Gender</i>			
<i>Female</i>	0.74	0.29-1.89	0.53
<i>Male</i>	reference category		

*= Statistically significant at $\alpha=0.05$

The next step was omitting the variable which had the highest p-value, which was gender in this model.

Table 5. Step 2 in developing the main effects model of potential risk factors for TB infection including reported smoking and Aboriginal status (n=103)

	Adjusted Odds Ratio	95% Confidence Interval	<u>p value</u>
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<i>Smoking Status</i>			
<i>Smoker</i>	2.03	0.71-5.80	0.19
<i>Non-Smoker</i>	reference category		
<i>Aboriginal Status</i>			
<i>Aboriginal</i>	0.52	0.18-1.46	0.21
<i>Non-Aboriginal</i>	reference category		
<i>Education</i>			
<i>Elementary Education</i>	2.79	0.96-8.08	0.59
<i>Secondary/Post-Secondary Education</i>	reference category		
<i>Hair Dying</i>			
<i>Hair Dye</i>	2.98	1.13-7.85	0.28
<i>No Hair Dye</i>	reference category		
<i>Alcohol Consumption</i>			
<i>Low/No Alcohol Consumption</i>	2.51	0.97-6.52	0.59
<i>High Alcohol Consumption</i>	reference category		

*= Statistically significant at $\alpha=0.05$

The next step was omitting alcohol from the model. When omitting alcohol from the model, the regression coefficient for aboriginal/smoker changed more than 10%, so alcohol was kept in the model as a confounder. The regression coefficient for aboriginal/smoker changed when removing both education and hair dying. All three were considered to be confounders and

retained in the final model to ensure unbiased estimates of the association between smoking and Aboriginal status on the risk of TB.

Table 6. Final main effects model examining the association between Aboriginal status and smoking with TB infection accounting for other potential risk factors (n=103)

	Adjusted Odds Ratio	95% Confidence Interval	<u>p value</u>
<i>Smoking Status</i>			
<i>Smoker</i>	2.03	0.71-5.80	0.19
<i>Non-Smoker</i>	reference category		
<i>Aboriginal Status</i>			
<i>Aboriginal</i>	0.52	0.18-1.46	0.21
<i>Non-Aboriginal</i>	reference category		
<i>Education</i>			
<i>Elementary Education</i>	2.79	0.96-8.08	0.59
<i>Secondary/Post-Secondary Education</i>	reference category		
<i>Hair Dying</i>			
<i>Hair Dye</i>	2.98	1.13-7.85	0.28
<i>No Hair Dye</i>	reference category		
<i>Alcohol Consumption</i>			
<i>Low/No Alcohol Consumption</i>	2.51	0.97-6.52	0.59
<i>High Alcohol Consumption</i>	reference category		

*= Statistically significant at $\alpha=0.05$

Of the five predictor variables, none were statistically significant. Smokers had an association with higher odds of TB infection (OR=2.03, 95% CI 0.71-5.80, p=0.19). Canadian-born Aboriginals had an association with lower odds of TB infection (OR=0.52, 95% CI 0.18-1.46, p=0.21). Smoking status, education, hair dyeing, and alcohol consumption all had extremely wide confidence intervals, meaning that the data may be too variable to elicit a precise estimate.

Chapter Five: Discussion

5.1 *Descriptive Statistics*

The purpose of this cross-sectional study was to observe the association of smoke exposure and tuberculosis-related outcomes in Saskatchewan by using hair samples. It examined 104 individuals who had been in contact with an infectious TB case. This study is unique because it examined hair samples to determine to how much smoke individuals were exposed. The majority of individuals were between the ages of 18 and 65; only one individual was over the age of 65.

Only four individuals from this study had TB (3.8% of the population). It is extremely important to note that three out of the four individuals who had Active TB were HIV positive. The reason this is important information is to consider is because HIV is one of the strongest risk for developing TB disease. Further discussion on HIV in this study can be found in the limitations section of this document. Nevertheless, all four individuals who developed TB disease were Canadian-born Aboriginal people. This mirrors the patterns in the province of Saskatchewan: the majority of TB cases in the province occur among Canadian-born Aboriginal people (55). Moreover, 3 of the 4 TB cases had developed the disease prior to the study. This means we cannot make any definitive remarks on the development of active TB from smoke exposure; this is because prior knowledge regarding smoking status and other risk factors is unknown in these individuals.

The difference in nicotine concentration between smokers and non-smokers was extremely large and statistically significant ($p=0.001$) (see Figure 4). The majority of non-

smokers had a nicotine concentration below 1ng/mg, whereas most smokers had a nicotine concentration in the range 2-15ng/mg. This supports the notion that smokers had more nicotine exposure than non-smokers, which was expected. Moreover, non-smokers who reported to have passive smoke exposure had more nicotine concentration than non-smokers who reported to have no passive smoke exposure (Figure 3).

Nearly half (49%) of women and 10% of men reported that they dyed their hair. Because hair dye may have played a significant role in shaping nicotine concentration (see limitations section), the nicotine concentration between smokers and non-smokers for individuals who dyed their hair or did not dye their hair was compared (as seen in Figure 5). There appears to be a significant difference between smokers who dyed their hair and did not dye their hair. The range of nicotine concentration was much lower for individuals who dyed their hair. The highest amount of nicotine found in smokers who did not dye their hair was just over 60ng/mg. The highest amount of nicotine found in smokers who did dye their hair was just over 20ng/mg. Most of the smokers who dyed their hair fell between 1-12ng/mg, whereas most smokers who did not dye their hair fell between 4-19ng/mg. A Wilcoxon test determined there was a significant difference between smokers who dyed their hair and smokers who did not dye their hair ($p=0.02$), meaning there was an association between hair dye and hair nicotine levels. There was no significant association found between non-smokers who did not dye their hair and non-smokers who did dye their hair. This was expected because the nicotine concentration found in non-smokers was so low, hair dye would only have made a subtle impact. It is possible that the difference between smokers who dyed their hair and did not dye their hair could be due to another variable at play. For example, people who dye their hair may care more about appearances and wash their hair more; this may wash away any nicotine from the ambient

environment. The difference could also be attributed to the impact of hair dye has on the hair shaft. Hair dye damages the hair shaft, which could limit the amount of nicotine that is stored in the hair.

Information regarding housing density was also collected for this study because crowding is a risk factor for TB transmission (54). According to a Canadian study, an increase of 0.1 persons per room increased the risk of two or more cases of TB in a community by 40% (56). After calculating housing density in this study, approximately 66% of individuals were living in high density housing (having 0.7 persons per room or higher). This is a significant portion of individuals to live in these conditions, especially because high density housing is a risk factor for TB. Canadian-born Aboriginals are known to live in high density housing (57). Housing density among ethnicities was examined to see if our data reflected findings in the literature. A boxplot was created to visually assess the difference among the three different ethnicities: Canadian-born Aboriginal, Canadian-born Non-Aboriginal, and Foreign-born (see Figure 6). There is a very noticeable difference among the three ethnicities. It is clear that Canadian-born Aboriginals have considerably higher housing densities than both Canadian-born Non-Aboriginal and Foreign-born. Most Canadian-born Aboriginals lived in high density housing, whereas most Canadian-born Non-Aboriginals lived in low density housing. This is a similar trend to what is reported in the literature (57). The foreign-born population was split evenly between high density housing and low density housing.

5.2 Research Question 1

The association between nicotine concentration and cigarettes consumed per day was not linear, so a quadratic term was added. The quadratic term reported cigarette consumption per

day was significantly associated with nicotine concentration. Higher reported cigarette consumption meant a higher nicotine concentration was found in the hair, whereas a lower reported cigarette consumption meant a lower nicotine concentration was found. It was expected that people who smoked more cigarettes would have a higher concentration of nicotine in their hair because they were exposed to more nicotine than people who smoked less or no cigarettes. Nevertheless, the last term in the quadratic equation ($y=0.91+1.35x-0.25x^2$) was negative, suggesting that individuals who reported consuming more cigarettes a day may have incorrectly reported the number of cigarettes they consumed in a day. Some individuals who smoked between 10-20 cigarettes a day had higher nicotine concentrations than individuals who smoked >30 cigarettes/day. This anomaly may have occurred for a few different reasons: it may have been an error in self-reporting cigarette consumption; it could also have been because these individuals smoked outside (this would decrease nicotine exposure); these individuals may smoke more per day, but inhale less nicotine due to the amount of nicotine in the cigarette or simply inhale less of the cigarette than others. Moreover, certain levels of reported cigarette smoking cluster (as seen in Figure 7). There was a lot of clustering amongst those smoking 10 cigarettes/day. This may be because 10 cigarettes/day is an easy estimate for people to report, especially if someone smokes less than a pack/day (approximately 25 cigarettes in a pack) and their cigarette consumption varies depending on the day. They may also report 10 cigarettes/day if they are a heavier smoker (smoking pack/day), but want to present themselves as a “lighter” smoker due to social criticism.

5.3 Research Question 2

Among individuals who had a TB infection, no significant relationship was found between smokers and an increased risk of active TB when being compared to non-smokers. Only four individuals developed the outcome, meaning that finding a statistical association between the two variables was challenging. The fact that three out of these four cases had previously developed TB ruled out identifying such a relationship. Nevertheless, other studies have concluded that smokers have an increased likelihood of developing active TB than non-smokers. One meta-analysis estimated that smokers were 2.3-2.7 times more likely to develop active TB than non-smokers (45). Another study looked a fairly large sample size (over 17,000 participants) and found that smokers had a 1.94 more chance of developing active TB than non-smokers when looking at individuals with positive TSTs (42). This study did not have similar findings, but our sample size was also significantly smaller than most studies. Moreover, active TB is something that takes time to develop, so future studies may want to have a longer timeframe in order to see who develops the outcome. Because this study took place over 14 months, data on development of active TB over time was limited.

5.4 Research Question 3

There was no statistically significant association between smoking and TB infection. A larger sample size may have been able to provide a better understanding of a possible relationship. Moreover, there was no statistically significant association between aboriginal status and TB infection. Nevertheless, the burden of TB in Canadian-born Aboriginals is much higher than the rest of the Canadian population. It is estimated that in 2011, the overall rate of TB infection and disease among Canadian-born Aboriginals was nearly six times the Canadian

rate (58); this study did not have similar findings. Once again, a larger sample size would have been able to give a better understanding of a possible relationship between Canadian-born Aboriginals and TB infection.

5.5 Other Findings

Working in the field on contact traces with the TB nurse proved to be a complicated task. Many people were difficult to contact, which made it especially difficult for the TB nurse to find certain individuals who were at higher risk of contracting TB. Patience became the most important attribute when performing contact traces. Some people would have a scheduled appointment with the TB nurse, but would not show up or answer their door. It would then require the nurse to make another effort to find this person who needed to be tested. It was equally important to be accommodating on contact traces. This meant travelling a far distance or changing our schedule around just to be able to meet someone. For future, bigger studies, it is recommended that active case finding be used (actively finding people who need to be tested, instead of them coming to those conducting the tests or being referred by a doctor).

Alternatively, the consent rate was quite high among individuals who were asked to participate in this study. This was very positive, as the interview and hair cutting process took time. Many of the questions on the interview were quite sensitive. The interview had to be approached with a very open mind and strong listening skills. It is a notable finding that most individuals were quite comfortable with donating hair samples for the purpose of research (everyone who was asked to donate a hair sample complied).

5.6 Limitations

Individuals asked to participate in this study were seen either in TB clinic or the field. Of the individuals in this study, 83 (80%) were seen in the field and 21 (20%) were seen in the clinic. Patients were brought to clinic because they were known to have a positive skin test, or they needed proper follow-up with one of the TB doctors. Because of this, individuals who were seen in clinic were not randomly selected; this reduces the external validity of the study, meaning that our conclusions are less likely to apply to the general population.

The cut-off for the TST was 5mm, which is the accepted practice among TB health professionals. Nevertheless, a cut-off of 5mm, as opposed to 10mm or 15mm, lowers specificity and increases sensitivity. A TST of 5mm could mean TB, but it may also be noise, such as a reaction to a previous vaccination. A TST of 15mm is almost certainly TB, as this cut-off minimizes any noise that may occur.

Thirteen individuals that were used in this study were found to have a previously positive recorded skin test. This means our data was limited because we were unsure of their smoking status during their previous positive TST. There was a section on the questionnaire dedicated to asking about past smoking history, but this was not the most accurate way to uncover past smoke exposure. Ideally, a hair sample would have been obtained at the first recorded positive TST, as this would have been the most accurate way of examining smoke exposure. For future studies, anyone who had a previous positive TST should not be eligible to participate in the study, unless a clear history of smoking and date of TST is provided.

Second-hand smoke exposure was not well documented during the questionnaire. Non-smokers were asked how often they were exposed to the tobacco smoke of others, but not if they

live with a smoker. Obtaining this information would have allowed us to compare non-smokers who live with smokers and smokers to see if there was a significant difference in TB infection between the two groups. This may have provided some interesting insight into the affect second-hand smoke has on TB infection/disease.

HIV was a factor that affected a number of individuals in this study (9.5% of individuals, 10/104). HIV plays a significant confounder when looking at the development of TB. This is because HIV is one of the strongest risk factors for developing TB disease. In hindsight, individuals who knew they were HIV positive should have been omitted from participating in the study.

Nearly half of the women in this study reported to dying their hair in the last six months. Research seems to be quite varied on the impact hair dye has on the uptake of nicotine concentration in hair. One study examined the use of hair dye and concluded that the chemicals used for dying hair lowered nicotine and cotinine levels in hair, but do not completely eliminate them (49). Another study looked at the effects of bleaching and hair dye on 8 samples of smokers. They found that the cuticle of the hair was not damaged after dying the hair, but that nicotine levels were reduced by 30% (49). It appears that cosmetic treatment of the hair does affect the nicotine in the hair. In this study, we compared four groups in a boxplot: non-smokers who do not dye their hair, non-smokers who dye their hair, smokers who do not dye their hair, and smokers who dye their hair. The comparison between the four groups suggests that there is a fairly significant difference in nicotine concentration levels between people who do and do not dye their hair.

Another limitation of this study was the sample size. The fact that only 104 subjects were recruited for this study really limited the amount of data and the associations that could be

made. A smaller sample size also meant wider confidence intervals, which may have lowered the significance of any result. It was difficult to calculate power analysis because the amount of people on contact traces, and how were available to be tested, varied throughout the year data was collected. Looking towards future studies, more time is needed to recruit participants, so that a larger sample size can be obtained.

5.7 Conclusion

Tuberculosis (TB) has been a major threat to humans for a very long time. Smoking has been singled out as a risk factor for contracting TB infection and progression to TB disease. Despite numerous medical advances with tuberculosis in recent years, only a limited number of studies have examined the effect that active and passive smoking may have on contracting TB infection and progression to TB disease. Even fewer studies have measured smoking with a method that does not completely rely on questionnaires. One of the main strengths of this study is that it asked individuals how much they smoked and took a sample of their hair to get an exact idea of nicotine exposure.

Although the sample size of this study was quite small compared to other studies looking for similar associations, there were a few interesting relationships that emerged from the data. The impact of hair dye on nicotine concentration was a relationship of interest. It appeared that hair dye had a significant impact on nicotine concentration. Reassuringly, there also appeared to be a strong association between reported cigarette consumption and nicotine concentration. Smoking and aboriginal status were not found to play a significant role in TB infection when building our full main effects model. Moreover, there was no association between smoking and active TB found. Lack of significance may have been caused from the small sample size.

Studies looking to build on this research will need a bigger sample size and to consider both HIV and hair treatment when gathering the data. Additionally, collecting data over a longer period of time could potentially mean stronger associations, as development of TB may be more closely followed.

Appendices

Informed Consent



PARTICIPANT INFORMATION AND CONSENT FORM

This Participant Information and Consent Form is for contacts of active TB cases in Saskatchewan, whom we are inviting to partake in a study project titled "The Association of Smoke Exposure and Tuberculosis in Saskatchewan".

Project title:

The Association of Smoke Exposure and Tuberculosis in Saskatchewan

Lead Investigator:

Dr. Nathaniel Osgood, Department of Computer Science, University of Saskatchewan, SK, Canada

Team members:

1. Dr. Vernon H. Hoepfner, Department of Medicine, University of Saskatchewan and Saskatchewan TB Control Program, SK, Canada
2. Dr. Assaad Al-Azem, Saskatchewan TB Control Program and Postdoctoral Fellow (VIDO), University of Saskatchewan, SK, Canada
3. Dr. Kristen Hassmiller Lich, Department of Health Policy and Management, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
4. Dr. Wael Al-Delaimy, Department of Family and Preventive Medicine, University of California San Diego, San Diego, CA, USA

Sponsoring or Collaborating organization(s)

1. Lupina Foundation (Sponsor)
2. Saskatchewan TB Control.

This Participant Information and Consent Form has two parts:

- Information Sheet (to share information about the study with you)
- Certificate of Consent (for signatures if you choose to participate)

Introduction

We are asking you to be part of a study to learn about the connection between smoking and TB. We want the facts in this form to help you understand what we are asking of you so that you can decide whether or not you want to be in this study. Please read this form and think of questions you might ask before deciding. Please take all the time you want and ask others about the study. You can say yes or no. It is your decision. Saying no will not affect the medical care that you need or get.

Purpose of the Study

Some people in our community have TB or have been in contact with TB. We hope to find out why some people have TB what is causing this. We want to find out the extent to which person's having breathed tobacco smoke can tell us whether they are at risk of TB. One way of measuring tobacco smoked or breathed is through hair where tobacco parts are stored. Therefore, we plan to take hair samples from you. We also want to give you a questionnaire that will give us facts about you to better understand whether tobacco smoke exposure might increase your risk for getting TB and (if you wish to allow it) for us to contact you if needed. The results of this study could:

- a. Help us to prevent TB before it starts and to quickly treat TB if it develops..
- b. Help us find out how tobacco smoke makes it easier to get TB.

Type of Study Methods

In this study we would like to talk to you and take a small hair sample that will take 45 minutes in total.

Participant Selection

We are asking you if you would like to be a part in this study because we believe that as a contact of a TB case, your hair sample and personal smoke exposure can help us understand TB and who gets it in Saskatchewan.

- *Do you know why we are asking you to take part in this study? Do you know what the study is about?*

Voluntary Participation

Joining this study is completely your decision. It is your choice whether to join or not. If you choose no, it will not affect you in any way.

- *If you decide not to take part in this study, do you know what your choices are? Do you know that you do not have to take part in this study, if you do not wish to? Do you have any questions?*

Procedures

If you agree to take part in this study, we are asking you to take part in three components of the study: A) Collection of information from the Saskatchewan TB Control database B) an interview and C) a hair sample collection.

You may stop participating in the interview at any time that you wish. You will be given an opportunity at the end of the interview to review your answers, and you can ask to change or remove any of the answers, if you do not agree with them or if you feel you were not understood correctly, or if you are no longer comfortable responding to that question.

A) Collection of information from the Saskatchewan TB Control database

The Saskatchewan TB Control program helps lead the fight against TB in the province. In order to allow for better TB treatments and to help prevent TB, The Saskatchewan TB Control program maintains a database of information on those who have gotten TB and their contacts. Because you are someone who came into contact of a TB case, there is already some information that was asked of you during the interview earlier that will be entered into the database. We would like to use this information for the study, so that we don't have to ask you all the necessary questions again. This information will help us get a better understanding as to whether smoking may be contributing to the chance and severity of TB in general. The information that we are hoping to collect includes the

following:

Birth date

Sex

Ethnicity

Whether you are a contact for another TB case down the road (for up to 10 years time)

Information on whether in the future you are diagnosed with TB (for up to 10 years time). If you are diagnosed, we will be collecting on including information on

When you are diagnosed

How serious a case of TB it is

How long it takes you to recover from TB when you are treated

If you pass away from other causes before the study completes, we would also like to know that

We are seeking permission to allow us to access this information from the Saskatchewan TB Control database for a period of up to 10 years from now.

B) Interview

We do the interview after we have delivery of a completed and signed copy of this Participant Information and Consent Form. This will be the interview using a questionnaire that includes a set of questions about smoke exposure, other illnesses, whether you dye your hair and employment, housing, education facts. We want to especially compare the smoke levels in your hair with what you tell us about breathing or smoking tobacco. Several of the questions will also be important for understanding the results of the hair sample analysis. For example, a history of liver problems or of hair dying could affect the tobacco levels that we measure in the hair.

During the interview, the interviewer (Dr. Assaad Al-Azem, a member of the research team who is also with Saskatchewan TB Control) will sit down with you in a comfortable place at the TB clinic. If you do not wish to answer any of the questions during the interview, you may say so and the interviewer will move on to the next question. Unless you ask for someone else to be there during the interview, no one else but the interviewer will be present. The information is confidential, and no one else except the study team will have access to the information that you give during your interview. No one will be able to link this information to your name.

C) Hair sample collection

The second part is the collection of a small, 10 mg hair sample (a group of hair strands half the thickness of a pencil when held together), cut by blunt-ended scissors from the lower back of your head. If you are concerned about this affecting your appearance, smaller amounts of hair can be taken from several places. This is a quick process that will only take few minutes.

Duration

The interview and the sample collection should take about 45 minutes in total.

- *If you decide to take part in the study, do you know how much time will the interview take? Where will it take place? If you agree to take part, do you know if you can stop participating? Do you know that you may not respond to the questions that you do not wish to respond to? Do you have any more questions?*

Potential Risks/Harm

There are no known harms associated with your being in this study. The only risk is inadvertent release of your personal health information. The researchers will take special precautions to ensure confidentiality and the risk is considered very small.

We are asking you to give us some personal and confidential information. You may not want to talk about some of the topics. You do not have to answer any question or take part in the interview if you

choose not to do so, and that is also fine. You do not have to give us any reason for not answering any question, or for choosing not to take part in the interview.

Benefits

There will be no direct benefit to you, but your joining will help us learn more about why people in our community get TB. so that we can better prevent and treat TB.

Compensation

If you choose to join the study, we will give you \$10 or a voucher to pay you for some of your time.

- *Did you correctly understand the purpose of the study and the benefits that you will have if you take part in the study? Do you know if the study will pay for some of your time lost, and do you know how much you will be paid? Do you have any other questions?*

Confidentiality

In Saskatchewan, the Health Information Protection Act (HIPA) protects the privacy of your personal health information. Your privacy will be respected. Your name will not be attached to any information, nor mentioned in any study report, nor be made available to anyone except the research team. It is the intention of the research team to publish results of this research in scientific journals and to present the findings at related conferences and workshops, but your identity will not be revealed.

We will not be sharing any facts about you to anyone outside of the study team. The information that we collect from this project will be kept private. Any information about you will have a number on it instead of your name, and even the study team will not be able to link that number or the information to your name. This means that all information from your hair or interview will not be able to be traced to you.

- *Did you understand the procedures that we will be using to make sure that any information that we collect about you will remain confidential? Do you have any more questions?*

Nothing that you tell us during the interview will be shared with anybody outside the study team, and nothing will be attributed to you by name. The knowledge that we get from this study will be shared with Saskatchewan TB Control, and used only to better prevent and control TB services in your community. We may also publish some of the results so that other interested people may learn from this study, and so that other communities can benefit from the results.

Right to Refuse or Withdraw

Your participation in this research is voluntary. You may withdraw from this study at any time. You do not have to provide a reason. Your future medical care will not be affected.

If you choose to enter the study and then decide to withdraw at a later time, all data collected about you during your enrolment will be deleted.

Who to Contact

If you have any questions, you can ask now by contacting us or later during the interview. If you wish to ask questions, you may contact the following project investigator:

Name: Dr. Assaad Al-Azem
Telephone number: 306-655-7485
E-mail: assaad.alazem@usask.ca

This proposal has been reviewed and approved by the University of Saskatchewan Ethics Review Committee. The Research Ethics Board is a group of individuals (scientists, physicians, ethicists,

lawyers and members of the community) that provide an independent review of human research studies

- *Do you know that you do not have to take part in this study if you do not wish to? You can say No if you wish to? Do you know that you can ask questions later, if you wish to?*

You can ask questions about any part of the study, if you wish to. If you do have any questions, we encourage you to contact us.

I have been asked to join a study about tobacco smoke and tuberculosis. I have read the information, or it has been read to me. I have had the chance to ask questions about it and any questions I have been asked have been answered to my satisfaction. I consent voluntarily to be a participant in this study.

Print Name of Participant _____

Signature of Participant _____

Date _____
Day/month/year

Print Name of Person Obtaining Consent _____

Signature of Person Obtaining Consent _____

Date _____
Day/month/year

Participant is unable to give written consent and has given verbal consent to participate in this study¹

I have witnessed the accurate reading of the Participant Information and Consent Form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness _____

Signature of witness _____

Date _____
Day/month/year

Please indicate whether you authorize the researcher(s) to contact you in the future. You are not obligated to participate in any future research

I authorize the researcher(s) to contact me in the future for research purposes.

Yes No

¹ A witness must sign (if possible, this person should be selected by the participant and should have no connection to the study team).

Participant Questionnaire

Participant Questionnaire

DEMOGRAPHICS SECTION

1. **DATE OF BIRTH:** _____
2. **GENDER:** F ___ M ___
3. **ETHNICITY:**
FN..... ___
Métis..... ___
Inuit..... ___
Caucasian..... ___
Other..... ___
4. **What is the highest education level you have attained?**
Elementary..... ___
Secondary..... ___
University/College..... ___
None..... ___

HAIR TREATMENT EXPOSURE SECTION

5. **In the past 6 months, did you dye/highlight/bleach your hair?**
YES ___
NO ___

TOBACCO SMOKE EXPOSURE SECTION

I am going to ask you some questions about your exposure to tobacco. Unless I say otherwise, I am asking about smoking tobacco, including (cigarettes, bidis, cigars, pipes).

6. **Do you currently smoke tobacco on a daily basis, less than daily, or not at all.**
DAILY ___ SKIP TO QUESTION 10

LESS THAN DAILY

NOT AT ALL SKIP TO QUESTION 8

7. Have you smoked tobacco daily in the past?

YES SKIP TO QUESTION 10

NO SKIP TO QUESTION 11

8. In the past, have you smoked tobacco on a daily basis, less than daily, or not at all?

INTERVIEWER – If respondent has done both “daily” and “less than daily” in the past then respond “DAILY.”

DAILY

LESS THAN DAILY

NOT AT ALL SKIP TO QUESTION 12

9. How long has it been since you last smoked daily?

___ YEARS

___ MONTHS SKIP TO QUESTION 13

10. How old were you when you first started smoking tobacco?

___ YEARS OLD

11. On average, how many cigarettes do you currently smoke on days that you smoke?

INTERVIEWER – If respondent reports doing the activity, but less than once per day, leave the field blank and check the lower entry field. If the respondent reports in packs or cartons, probe to find out how many are in each and calculate total number.

___ PER DAY, or

___ mark here if less than 1 per day but more than 0

12. In the past week, approximately how many times have you been exposed to the tobacco smoke of others at home, work, or in public places (that is, where exposure is for a minimum of five consecutive minutes each time)?

NOT AT ALL

A FEW TIMES PER DAY ON SOME DAYS

MANY TIMES PER DAY ON SOME DAYS ___

A FEW TIMES PER DAY ON MOST DAYS ___

MANY TIMES PER DAY ON MOST DAYS ___

13. Do you currently use smokeless tobacco (including, for example, spit or chewing tobacco) on a daily basis, less than daily, or not at all?

DAILY ___

LESS THAN DAILY ___

NOT AT ALL ___

14. How many rooms other than closets/bathrooms/storage space are there in your current dwelling?

15. How many people in total currently reside in your dwelling?

CO-MORBIDITIES/ RISK FACTOR SECTION

Now I'd like to ask about certain chronic health conditions which [you/FNAME] may have. We are interested in "long-term conditions" which are expected to last or have already lasted 6 months or more and that have been diagnosed by a health professional.

16. Have you ever been diagnosed with a liver condition including (hepatitis, liver cirrhosis, cancer, and jaundice)?

YES ___ Condition _____

NO ___

17. Have you ever been diagnosed with diabetes?

YES ___ Type _____

NO ___

18. How old were you when you were first diagnosed with diabetes?

19. Have you ever been diagnosed with a kidney disease?

YES ___ Condition _____

NO ____

20. Have you been diagnosed or been informed by a health professional that you have any other health condition (such as high blood pressure, heart problem, chronic bronchitis, chronic obstructive pulmonary disease)?

YES ____ Condition _____

NO ____

Now I would like to ask some questions about alcohol consumption

When we use the word 'drink' it means:

- one bottle or can of beer or a glass of draft
- one glass of wine or a wine cooler
- one drink or cocktail with 1 and a 1/2 ounces of liquor.

21. During the past 12 months, have had a drink of beer, wine, liquor or any other alcoholic beverage?

YES ____

NO ____

22. During the past 12 months, how often did you drink alcoholic beverages?

Less than once a month..... ____

Once a month..... ____

2 to 3 times a month..... ____

Once a week..... ____

2 to 3 times a week..... ____

4 to 6 times a week..... ____

Every day..... ____

23. How often in the past 12 months have you had 5 or more drinks on one occasion?

Never..... ____

Less than once a month..... ____

Once a month..... ____

2 to 3 times a month..... _____
Once a week..... _____
More than once a week..... _____

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